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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/650,592	08/27/2003	Noubar B. Afeyan	COTH-P01-001	7920

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EXAMINER	
MEAH, MOHAMMAD Y	
ART UNIT	PAPER NUMBER
1652	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/29/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/650,592	AFEYAN ET AL.	
	Examiner	Art Unit	
	Mohammad Meah	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-5, 7-17, 25-7, 29, 31, 33, 35, 37-38, 40-44, 52, 58, 66 69-70, 72, 74, 76, 78, 80, 82, 84, 86, 91, 93, 95, 97, 99 101, 107-108, 113, 115, 117, 119, 127-134 and 156* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 10/2/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,4,5,7-17,25,29,31,33,35,37,38,40-44,52,58,66,69,70,72,74,76,78,80,82,84,86,91,93,95,97,99,101,107,108,113,115,117,119,127-134 and 156.

DETAILED ACTION

Claims 1-2, 4-27, 29,, 31, 33, 35, 37-38, 40-44, 52-53, 58 60, 66, 68-82 84-86, 90-102, 104 (2nd), 107-108, 113-120 and 127-134 were examined in the previous action. With supplemental amendment of this application, the applicant, on dates 9/29/06, amended claims 1, 4, 5, 7-17, 25-27, 29, 31, 33, 35, 37-52, 56, 58, 61, 62, 64, 66, 69, 70, 72, 74, 76, 78, 80, 82, 84, 86-88, 91, 93, 95, 97, 99, 101,103-111, 113,115, 117, 119, 121,123, 125, 127-138, 147, 148, 150, 151, and 156 (renumbered from the former 2na Claim 104). Among them, claims 39, 45-51, 56, 61, 62, 64, 87, 88, 103-106, 109-111,121,123, 125, 135-138, 147, 148,150, and 151 are directed to non-elected inventions or species, and are withdrawn from further consideration. Claim 2, 3, 6, 18-24, 28, 30, 32, 34, 36, 53-55, 57, 59, 60, 63, 65, 67, 68, 71, 73, 75, 77, 79, 81, 83, 85, 89, 90, 92, 94, 96, 98, 100, 102, 112, 114, 116, 118, 120, 122, 124, 126, 139-146,149, and 152-155 are canceled. Therefore claims 1, 4-5, 7-17, 25-27, 29, 31, 33, 35, 37-38, 40-44, 52, 58, 66 69-70, 72, 74, 76, 78, 80, 82, 84, 86, 91, 93, 95, 97, 99 101, 107-108, 113, 115, 117, 119, 127-134 and 156 are for further examination.

Claim Rejections

35 U.S.C 112

35 USC 112 2nd paragraph

Claims 1, 5, 7-17, 25-27, 29, 31, 33, 35, 37-38, 40-44, 52, 58, 66, 69, 70, 72, 74, 76, 78, 80, 82, 84, 86, 91, 93, 95, 97, 99, 101,107, 108, 113,115, 117, 119, 127-134 and 156 remain rejected under USC 112 *2nd paragraph* requirement

Because the recitation of the term "potency" makes these claims confusing.

Applicants arguments at page 7 of their amendments against rejection of claims 1, 5 and 10-11 under 35 U.S.C 112, 2nd paragraph requirement are acknowledged but not found persuasive because: Applicant appears to argue that potent or potency is term used in biochemistry for "enzyme activity". If that is so then applicant should replace "potency " by "enzyme activity" a commonly known term in art.

35 U.S.C 112

Written Description requirement

Rejection of claims 1, 4-5, 7-17, 25-7, 29, 31, 33, 35, 37-38, 40-44,52, 58, 66 69-70, 72, 74, 76, 78, 80, 82, 84, 86, 91, 93, 95, 97, 99 101, 107-108, 113, 115, 117, 119, 127-134 and 156 under USC 112 1st paragraph Written Description requirement is withdrawn after amendment of the claims by the applicant.

Enablement requirement

Rejection of claims 25-77, 29, 31, 35, 37-38, 40-44,52, 58, 66 69-70, 72, 74, 76, 78, 80, 82, 84, 86, 91, 93, 95, 97, 99, 101, 107-108, 113, 115, 117, 119, 127-134 and 156 under USC 112 1st paragraph enablement requirement is withdrawn after amendment of the claims by the applicant.

However Claims 1,4, 10-17, 33, 86, 131 and 132 remain rejected under USC 112 1st paragraph enablement requirement.

Claims 1, 10-17, 33 recite many kinetic properties (with specific kinetic parameters) of fusion proteins. As explained in the previous office action, the scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number adzymes or fusion proteins attached to these kinetic parameters. Since specific kinetic parameter depend on type of individual protease, individual targeting domain (antibody or protein) it is linked to as well as on the type of conjugation with individual linker peptide and individual substrate polypeptide the adzyme acts on, achievement of desired kinetic values for the broad class of adzymes (made via conjugation of any protease conjugated through board class of linker polypeptides with broad class of targeting domains) acting on board class of substrates is highly unlikely. Specification disclose kinetic parameters for few such adzymes.

Claims 4 and 86 remain rejected under USC 112 1st paragraph enablement requirement.

Claims 4 and 86 recite an adzyme that catalyze the proteolytic cleavage of any substrate polypeptide producing any product which inhibits the substrate or the proteolytic cleavage of adzyme. The claims broadly recite the use of **any** substrate polypeptide, which is cleaved by adzyme to produce any product that inhibits the substrate binding or adzyme cleavage. The specification fails to describe how any cleavage-product of any substrate polypeptide inhibits

the substrate or the proteolytic cleavage of adzyme. The specification fails to describe in any fashion the physical and/or chemical properties of the claimed class of substrates and their by-products as discussed above. As the structure of the claimed substrates and their by-products are not defined in any way, one of ordinary skill in the art would not be able to make and use any of such substrates without undue experimentation to first find what substrate and their by-product in fact fall within the claimed class. Furthermore, the claimed class of substrates and their by-products is likely to include many compounds, which one of ordinary skill in the art would be unable to make and use without undue experimentation, even if it was known or expected that the substance be within the scope of the claims.

Claims 131-132 recite an adzyme preparation wherein autocatalytic proteolysis is inhibited by any means or especially by inclusion of a reversible inhibitor but it is not clear that there are available reversible inhibitors for any protease nor are other means of formulating an adzyme composition to present auto proteolysis is taught.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any substrate and their by-product. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of substances having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

CLAIM Rejection - 35 U.S.C 102

The 102 rejections of claims 1, 4-5, 7-17, 25-27, 29, 31, 33, 35, 37-38, 40-44,52, 58, 66 69-70, 72, 74, 76, 78, 80, 82, 84, 86, 91, 93, 95, 97, 99 101, 107-108, 113, 115, 117, 119, 127-134 and 156 under 35 U.S.C. 102 using Holvoet et al. (JBC1991, vol.266, pp 19717-19724) or Davis et al. (WO 00/64485) or Chen et al. (US 2003/0068792), of the previous office action are still remained applicable.

Claims 1, 5, 7-17, 25, 35, 37-38, 40-42, 44, 52, 66, 69-70, 84, 91, 93, 95, 97, 107-108, 127, 133 are rejected under 35 U.S.C. 102(b) as being anticipated by Holvoet et al. (JBC1991, vol.266, pp 19717-19724).

Holvoet et al. teaches (page I paragraph I and 2) fusion proteins of plasminogen activator (Urokinase – a serine protease) is fused with fibrin-specific antibody (variable region Fv) molecule. The resulting fusion protein shows 2.5-13 fold increase of the fibrinolytic potency. Fusion protein of single chain Urokinase fusion to antibody had the following kinetic parameters: *Ka* = 5.5 X 10^{9} M^{-1} *Km* = 12 microM and *Kcat* = 0.12 X 10^{-6} M^{-1} $/sec^{-1}$ for the fusion protein compare to 0.02 X 10^{-6} M^{-1} $/sec^{-1}$ for unconjugated enzyme.. This fusion protein target cells (in this case blood clot) than cleave plasminogen to release active plasmin (an enzyme) resulting plasmin in turn inhibit/digest extracellular signalling molecules, act on cytokine transforming growth factor or lyse clot.

Claims 4-5, 7-9, 11-17, 31, 35, 37-38, 40-44, 52, 58, 66, 69-70, 72, 74, 76, 78, 80, 82, 84, 86, 91, 93, 95, 97, 99, 101, 107-108, 113, 115, 117, 119, 127-128 and 156 are rejected

under 35 U.S.C. 102(b) as being anticipated by Davis et al. (WO 00/64485). Davis et al. teach fusion proteins wherein enzymes (serine protease, chymotrypsin, etc) which catalyze degradation of a specific target, are conjugated to binding partners wherein the binding partner is an antibody (immunoglobulin), peptide or protein, receptor or chemical with or without a linker and resulting fusion protein has greater (catalytic or more than one) activity than the unconjugated molecule. The chimeric protein of Davis et al. bind to the target and the antagonize/inhibit/degrade a wide variety of receptors and/or intermediary signaling molecules such as cytokines, EGF-like factors, receptor of TNF and TNFα. Davis et al. use the fusion protein as a pharmaceutical composition wherein the targeted enzyme is protease and use the pharmaceutical composition for autoimmune disease, infectious diseases, cancer, etc.

Claims , 4-5, 7-8, 11-17, 25-27, 31, 35, 37-38, 40-44, 52, 58, 60, 66, 69-70, 72, 74, 76, 78, 80, 82, 84, 86, 91, 93, 95, 97, 99, 101, 107-108, 113, 115, 117, 119, 127-128 and 156 are rejected under 35 U.S.C. 102(e) as being anticipated by Chen et al. (US 2003/0068792). Chen et al. teach fusion proteins wherein enzyme (beta lactamase, serine protease, protease that resistant to protease inhibitors and etc) conjugated with or without a linker to immunoglobulin or antibody, peptides, or chemical to the target proteins such as kinases, lipases, and tumor or cancerous cells via with or without a linker and the resulting fusion protein bind to the target better than unconjugated enzyme. The fusion protein of Chen et al. bind to the target and then inhibit/degrade a wide variety of targets associate with variety of hormones, receptors and/or intermediary signaling molecules such as cytokines, EGF-like factors, receptor of TNF and TNFα. etc. Chen et al. use the fusion protein as a pharmaceutical composition wherein the

targeted enzyme is protease and use the pharmaceutical composition for autoimmune disease, infectious diseases, cancer, etc.

Claims 1, 10-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Holvoet et al. (JBC1991, vol.266, pp 19717-19724) and Chen et al. (US 2003/0068792).

Holvoet et al. teaches (page I paragraph I and 2) fusion proteins of plasminogen activator where fibrin-specific antibody (variable region Fv) molecule is fused with single chain Urokinase (a serine protease). The resulting fusion protein shows 2.5-fold increase of the fibrinolytic potency. Although Holvoet et al. does not disclose all the specific kinetic properties of the instant claims, the fusion protein had a 2.5-13 fold increase of the fibrinolytic potency compared to unconjugated enzyme. Fusion protein of single chain Urokinase fusion to antibody had the following kinetic parameters: $Ka = 5.5 \times 10^{9}\ M^{-1}$ Km = 12 microM and $Kcat = 0.12 \times 10^{-6}\ M^{-1}/sec^{-1}$ for the fusion protein compare to $0.02 \times 10^{-6}\ M^{-1}/sec^{-1}$ for unconjugated enzyme. In view of the above characteristics of the fusion protein of Holvoet, a skilled artisan would expect that the fusion protein of Holvoet et al. would meet the kinetic parameters recited in claims 1, 10-17.

Chen et al. teach fusion proteins wherein enzyme (beta lactamase, serine protease, protease that resistant to protease inhibitors and etc) conjugated to ligand binding domain or protein or peptide ,antibody or chemical to target proteins (such as kinases, lipases , etc) or tumor or cancerous cells via with or without a linker and the resulting fusion protein bind to the target better than unconjugated enzyme. The fusion protein of Chen et al. bind to the target and then inhibit/degrade a wide variety of targets associate with variety of hormones, receptors and/or intermediary signaling molecules such as cytokines, EGF-like factors, receptor of TNF

and TNFα. etc. Although Chen et al. does not disclose the specific kinetic properties, they teach fusion protein which bind to the target 10-10000 better than unconjugated enzyme without substantially losing the enzymatic activity of the unconjugated enzyme. In view of the above characteristics of the fusion protein of Chen, a skilled artisan would expect that the fusion protein of Chen et al. would meet the specified kinetic properties of the instant claims.

Since the office does not have facilities to test the characteristics of a prior fusion protein and reasonable basis exists for believing that the prior art fusion protein has all the recited characteristics, it is the burden of the applicant to show that the fusion protein of the prior art lack the characteristics.

Applicant's argument, that Holvoet et al. (JBC1991, vol.266, pp 19717-19724) or Davis et al. (WO 00/64485) or Chen et al. (US 2003/0068792), does not teach the fusion proteins that are resistant to autoproteolytic cleavage is not found to be persuasive because although they did not mention the resistivity to auto proteolysis, they also did not mention that they are labile to proteolysis and furthermore as their fusion protein are stable enough to show protease activity to cleave substrate polypeptide shows some inherent resistibility to cleavage. Amended claims 1, 4-5, 7-17, 25-7, 29, 31, 33, 35, 37-38, 40-44,52, 58, 66 69-70, 72, 74, 76, 78, 80, 82, 84, 86, 91, 93, 95, 97, 99 101, 107-108, 113, 115, 117, 119, 127-134 and 156 are therefore rejected under 35 U.S.C. 102(b) using Holvoet et al. (JBC1991, vol.266, pp 19717-19724) or Davis et al. (WO 00/64485) or Chen et al. (US 2003/0068792

Chen et al. teach fusion proteins wherein enzyme (beta lactamase, serine protease, protease that resistant to protease inhibitors and etc) conjugated with or without a linker to immunoglobulin or fragment or antibody to the target proteins such as kinases, lipases , and tumor or cancerous cells via with or without a linker and the resulting fusion protein bind to the target better than unconjugated enzyme. The fusion protein of Chen et al. bind to the **target and then inhibit/degrade a wide variety of targets associate with variety of hormones, receptors and/or intermediary signaling molecules such as cytokines, EGF-like factors, etc**. Chen et al. use the fusion protein as a pharmaceutical composition wherein the targeted enzyme is protease and use the pharmaceutical composition for autoimmune disease, infectious diseases, cancer, etc. Although Chen et al. does not disclose the specific kinetic properties, they teach fusion protein which bind to the target 10-10000 better than unconjugated enzyme without substantially losing the enzymatic activity of the unconjugated enzyme

Guo et al. teach fusion proteins wherein an enzyme (ASNase) is conjugated to an immunoglobulin or fragment or antibody (scFV) by a linker polypeptide $(Gly_4Ser)_3$.

Whitcomb et al. (US PAT6406846) teach mesotrypsin – a trypsin-like protease (page 10 1st paragraph) that is fairly stable to proteolytic cleavage and also teach that mesotrypsin rapidly degrades and inactivate zymogens and other polypeptides.

Sallberg et al. (US 6960569) teach fusion protein of mutated NS3/4A protease domain of HCV conjugated to antibody or other protein wherein fusion protein is resistant to proteolytic cleavage (mutation of breaking point residues of protease causes resistance to the proteolytic cleavage)

fusion protein binds target cells (in this case blood clot) then cleaves plasminogen to release active plasmin (an enzyme) resulting plasmin in turn inhibit/digest extracellular signalling molecules, act on cytokine transforming growth factor or lyse clot. Holvoet et al. teaches (page I paragraph I and 2) fusion proteins of plasminogen activator where fibrin-specific antibody (variable region Fv) molecule is fused with single chain Urokinase (a serine protease). The resulting fusion protein shows 2.5-fold increase of the fibrinolytic potency. **Although Holvoet et al. does not disclose all the specific kinetic properties of the instant claims, the fusion protein had a 2.5-13 fold increase of the fibrinolytic potency compared to unconjugated enzyme. Fusion protein of single chain Urokinase fusion to antibody had the following kinetic parameters:** $Ka = 5.5 \times 10^{9}\ M^{-1}$ $Km = 12$ **microM and** $Kcat = 0.12 \times 10^{-6}\ M^{-1}/sec^{-1}$ **for the fusion protein compare to** $0.02 \times 10^{-6}\ M^{-1}/sec^{-1}$ **for unconjugated enzyme.**

Davis et al. teach fusion proteins wherein enzymes (serine protease, chymotrypsin, etc) which catalyse degradation of a specific target are conjugated to binding partners wherein the binding partner is an antibody (immunoglobulin) **to the target with or without a linker and resulting fusion protein** has greater (catalytic or more than one) activity than the unconjugated molecule. The chimeric protein of Davis et al. bind to the target and the antagonize/inhibit/degrade a wide variety of receptors and/or intermediary signaling molecules such as cytokines, EGF-like factors, etc. Davis et al. use the fusion protein as a pharmaceutical composition wherein the targeted enzyme is protease and use the pharmaceutical composition for autoimmune disease, infectous diseases , cancer, etc.

Chen et al. teach fusion proteins wherein enzyme (beta lactamase, serine protease, protease that resistant to protease inhibitors and etc) conjugated with or without a linker to immunoglobulin or fragment or antibody to the target proteins such as kinases, lipases , and tumor or cancerous cells via with or without a linker and the resulting fusion protein bind to the target better than unconjugated enzyme. The fusion protein of Chen et al. bind to the **target and then inhibit/degrade a wide variety of targets associate with variety of hormones, receptors and/or intermediary signaling molecules such as cytokines, EGF-like factors, etc**. Chen et al. use the fusion protein as a pharmaceutical composition wherein the targeted enzyme is protease and use the pharmaceutical composition for autoimmune disease, infectious diseases, cancer, etc. Although Chen et al. does not disclose the specific kinetic properties, they teach fusion protein which bind to the target 10-10000 better than unconjugated enzyme without substantially losing the enzymatic activity of the unconjugated enzyme

Guo et al. teach fusion proteins wherein an enzyme (ASNase) is conjugated to an immunoglobulin or fragment or antibody (scFV) by a linker polypeptide $(Gly_4Ser)_3$.

Whitcomb et al. (US PAT4510251) teach mesotrypsin – a trypsin-like protease (page 10 1st paragraph) that is fairly stable to proteolytic cleavage and also teach that mesotrypsin rapidly degrades and inactivate zymogens and other polypeptides.

Sallberg et al. (US 6960569) teach fusion protein of mutated NS3/4A protease domain of HCV conjugated to antibody or other protein wherein fusion protein is resistant to proteolytic cleavage (mutation of breaking point residues of protease causes resistance to the proteolytic cleavage)

As such it would have been obvious to one of ordinary skill in the art to use mesotrypsin – a trypsin-like protease that is fairly stable to proteolytic cleavage as taught by Whitcomb et al. or mutation of protease as taught by Sallberg and conjugate said proteases by a linker as taught by Guo et al. to targeting domain as taught by Holvoet et al. (JBC1991, vol.266, pp 19717-19724) or Davis et al. (WO 00/64485) or Chen et al. (US 2003/0068792) and use the resulting adzyme to inactivate substrate polypeptides by catalyzing the proteolytic cleavage of the said substrate polypeptide.

Claim 119 is directed to an adzyme wherein targeting moiety is soluble portion of a TNFα receptor and antibody binds to TNFα.

As explained above it would have been obvious to one of ordinary skill in the art to use mesotrypsin – a trypsin-like protease that is fairly stable to proteolytic cleavage as taught by Whitcomb et al. or mutation of protease as taught by Sallberg and conjugate said proteases by a linker as taught by Guo et al. to targeting domain of **antibody** (claim as taught by Holvoet et al. (JBC1991, vol.266, pp 19717-19724) or Davis et al. (WO 00/64485) or Chen et al. (US 2003/0068792) and use the resulting adzyme to inactivate substrate **polypeptide such as TNFα (claim 113)** by catalyzing the proteolytic cleavage of the said substrate polypeptide as TNFα is clearly taught as a preferred target by both Davis et al. (page 29) and Chen et al.(paragraph 471). It would have been also obvious to use soluble portion of a TNFα receptor and antibody binds to TNFalpha combination as a targeting moiety for the said adzyme and use it to cleave the TNFalpha substrate.

Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 4 and 5 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 35, 2 and 19 of copending Applications No.10792498 and 10650591. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 4 of instant application comprises an adzyme comprising catalytic domain that catalyzes a chemical reaction involving substrate(s) and converting the substrate to product(s) wherein the resulting product(s) inhibit or antagonize to the substrate activity. Claim 5 of instant application comprises an adzyme comprising a fusion protein of catalytic domain fused with a

targeting moiety, wherein said fusion protein is resistant to cleavage by the catalytic domain, and said catalytic domain cleaves peptide bond of a substrate. Claims 35 of copending application 10,650591 and 10792498 comprises an adzyme comprising any protease as catalytic domain, fused with a targeting moiety, wherein said adzyme acts on the substrate to produce product(s) wherein resulting product(s) is an antagonist to the substrate, while claims 2 and 19 of the copending applications recite an adzyme comprising a protease fused with a targeting moiety wherein said fusion is resistant to cleavage by said protease. As such claims 4 and 5 of the instant application differ from claims 35 and 2 or 19 of the copending applications only in the scope of catalytic domains present in the claimed adzyme. As the adzymes of claims 35, 2 and 19 of the copending applications are fully encompassed within claims 4 and 5 herein, claims 35, 2 and 19 of the copending applications anticipate claims4 and 5 of the instant application.

Claims 1, 7-9, 18-27, 29, 31, 33, 35, 37-38, 40-44, 52-53, 58, 60, 66, 68-70, 72, 74, 76, 78, 80, 82, 84, 86, 90-91, 93, 95, 97, 99, 101, 107-108 113, 115, -1117, 119 and 127-134, are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-41 of copending Applications No.10792498 and 10650591. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical,

they are not patentably distinct from each other.

Claim 1 of instant application comprises an adzyme comprising catalytic domain that catalyzes a chemical reaction involving substrate(s) and converting the substrate to product(s) and said adzyme is more potent than the catalytic moiety or targeting moiety with respect to the said reaction towards the substrate. Claim 1 instant application differs in scope from claims 6-13 of copending applications 10792498 and 10650591 in that claim 1 herein is broader in scope comprising any enzyme in catalytic domain and reacting on any substrate.

Claims 1-2 of copending application 10,650591 and 10792498 comprises an adzyme comprising protease or serine protease as catalytic domain, fused with a targeting moiety, acts on any substrate polypeptide and said adzyme is resistant to cleavage by catalytic domain, claim 18 of copending applications recite the adzyme to cotranslational fusion protein encoded by a recombinant nucleic acid, claims 20-22 of the copending application limits the adzyme acts on substrate that present in biological fluid or blood of an animal and so on. As such these claims differ from claim 1 herein in the scope of enzyme present in the catalytic domain and that claim 1 herein recites the kinetic parameters of said adzyme. Claims 1, 7-9, 18-27, 29, 31, 33, 35, 37-38, 40-44, 52-53, 58, 60, 66, 68-70, 72, 74, 76, 78, 80, 82, 84, 86, 90-91, 93, 95, 97, 99, 101, 107-108 113, 115, -1117, 119 and 127-134 can not be considered patentably distinct over claims 1-41 of copending Applications No.10792498 and 10650591, when there is a specifically recited embodiment of corresponding applications that support claims 1-41 therein that would anticipate claims 1 and dependent claims, 7-9, 18-27, 29, 31, 33, 35, 37-38, 40-44, 52-53, 58, 60, 66, 68-

70, 72, 74, 76, 78, 80, 82, 84, 86, 90-91, 93, 95, 97, 99, 101, 107-108 113, 115, -1117, 119 and 127-134 herein. Alternatively, 1, 7-9, 18-27, 29, 31, 33, 35, 37-38, 40-44, 52-53, 58, 60, 66, 68-70, 72, 74, 76, 78, 80, 82, 84, 86, 90-91, 93, 95, 97, 99, 101, 107-108 113, 115, -1117, 119 and 127-134 herein cannot be considered patentably distinct over claims 1-41 of copending 10650591 and 10792498, when there is a specifically disclosed embodiment in copending 10650591 and 10792498 that supports claims 1-41 of that application and falls within the scope of instant claims herein because it would have been obvious to one having ordinary skill in the art to select the specific adzyme of such as, prothombin/scFv αHa, trypsin/sp55, etc, substrate such as polypeptide, hormone, growth factor, cytokine, etc, disclose in 10650591 and 10792498 to practice claims 1-41 of the copending application.

One having ordinary skill in the art would have been motivated to do this because that embodiment is disclosed as being a preferred embodiment within claims 1-41 of the copending application NO: 10650592 and 10792498.

Claims 10-17 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2, 4, 6-13, 21-25 of copending Applications No.10792498 and 10650591. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 1 of instant application comprises an adzyme comprising catalytic domain that catalyzes a chemical reaction involving substrate(s) and converting the substrate to product(s) and said adzyme is more potent than the catalytic moiety or targeting moiety with respect to the said reaction towards the substrate. Claim 1 instant application differs in scope from claims 6-13 of copending applications 10792498 and 10650591 in that claim 1 herein is broader in scope comprising any enzyme in catalytic domain and reacting on any substrate. Claim 1, 4-6 of the copending application further differ in scope from the instant claims in that claim 1 of the copending application recites specific kinetic parameters of the adzyme, claim 4 of the copending application recites that the product produced by the action of the enzyme on the substrate is an antagonist of the substrate and claim 5 of the copending application recites that adzyme is resistant to cleavage by the catalytic domain.

Claims 1-2 of copending application 10,650591 and 10792498 comprises an adzyme comprising protease or serine protease as catalytic domain, fused with a targeting moiety wherein said protease acts on extracellular signaling molecular substrate polypeptide and dependent claims 6-13 of copending applications 10792498 and 10650591 limit the scope of the adzymes of the claims to specific kinetic parameters, dependent claims 21-25 copending applications 10792498 and 10650591 limit the scope of the adzymes to specific substrates such as EGF-like factors, inflammatory cytokine, etc and so on. Claims 10-17 can not be considered patentably distinct over claims 1-2, 4, 6-13, 21-25 of copending Applications No.10792498 and 10650591, when there is a specifically recited embodiment of corresponding applications that

support claims 1-2, 4, 6-13, 21-25 therein that would anticipate claims 1 and dependent claims 10-17 herein. Alternatively, Claims 10-17 herein cannot be considered patentably distinct over claims 1-2, 4, 6-13, 21-25 of copending 10650591 and 10792498, when there is a specifically disclosed embodiment in copending 10650591 and 10792498 that supports claims 1-2, 4, 6-13, 21-25 of that application and falls within the scope of instant claims herein because it would have been obvious to one having ordinary skill in the art to select the specific adzyme of prothombin/scFv αHa, trypsin/sp55, and said substrate selected from EGF-like factors cytokine, etc disclose in 10650591 and 10792498 and to practice claims 1-2, 4, 6-13, 21-25 of the copending application.

One having ordinary skill in the art would have been motivated to do this because that embodiment is disclosed as being a preferred embodiment within claims 1-2, 4, 6-13, 21-25 of the copending application NO:10650592 and 10792498.

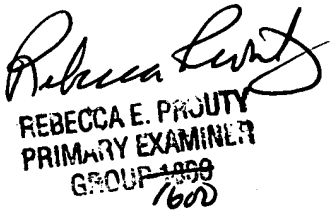
THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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Examiner, Art Unit 1652

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